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Activity of Ertapenem and Comparators against Gram-positive and –negative Anaerobes in Europe, 2010-2011

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Revised Abstract

Background: Anaerobic bacteria are frequently involved in intra-abdominal infections (IAI), and have remained largely susceptible to many antimicrobics approved for use against them. Ertapenem, a class I carbapenem, is indicated for use in IAI as well as other types of infections. There have been many reports on the activity of ertapenem and comparators against aerobic pathogens from the Study for Monitoring Antimicrobial Resistance Trends (SMART), but that surveillance program does not include anaerobic isolates. The present analysis was undertaken to ascertain the *in vitro* activity of ertapenem and comparators against a relatively large collection of anaerobes collected recently in Europe. **Methods:** 974 anaerobic isolates collected in 2010-2011 from a variety of specimen types (including, but not limited to, IAI) in the UK, Germany, France, Hungary, Czech Republic, and Belgium were tested at the IHMA central laboratory in Schaumburg, IL, USA using CLSI agar dilution methodology; MICs for ertapenem, cefoxitin (gram-negatives only), clindamycin, meropenem, metronidazole, penicillin (gram-positives only), piperacillin-tazobactam, and tigecycline were interpreted using EUCAST and CLSI guidelines. **Results**: 400 *Bacteroides* (incl. 265 *B. fragilis*), 248 *Clostridium* (incl. 151 *C. difficile*), 169 *Prevotella*, 72 *Peptostreptococcus*, 46 *Finegoldia magna*, 21 *Peptoniphilus asaccharolytica*, and 18 *Anaerococcus* spp. were tested. Percent susceptible values using EUCAST and CLSI breakpoints (FDA in the case of tigecycline), and MIC_{50}/MIC_{90} are shown in the following table:

Drug	EUCAST *C. difficile*	EUCAST Others	CLSI All	MIC_{50}	MIC_{90}
Ertapenem	-	96.0%	97.9%	0.12 mg/L	2 mg/L
Cefoxitin	-	-	94.2%[1]	4 mg/L	16 mg/L
Clindamycin	-	77.1%	75.3%	0.5 mg/L	>8 mg/L
Meropenem	-	97.2%	98.7%	≤0.06 mg/L	1 mg/L
Metronidazole	98.7%[2]	100%	100%	0.5 mg/L	2 mg/L
Penicillin	-	65.2%[3]	71.7%[3]	≤0.25 mg/L	2 mg/L
Piperacillin/Tazobactam	-	97.0%	99.7%	0.12 mg/L	8 mg/L
Tigecycline	98.0%[2]	-	99.5%[4]	≤0.06 mg/L	0.5 mg/L

[1]Gram-neg only
[2]Epidemiologic cutoff; no clinical breakpoints
[3]Gram-pos only
[4]FDA breakpoint; no CLSI breakpoint exists

Conclusions: Except for clindamycin and penicillin, all drugs tested inhibited ≥96% of the isolates. Although EUCAST breakpoints were lower than CLSI's for all drugs except clindamycin, % susceptible values were within 0-7% of each other. Ertapenem's *in vitro* activity against this collection of anaerobes was essentially equivalent to that of meropenem, metronidazole, piperacillin/ tazobactam, and tigecycline.

Introduction

Anaerobic bacteria are frequently involved in intra-abdominal infections (IAI), and have remained largely susceptible to many antimicrobics approved for use against them. Ertapenem, a class I carbapenem, is indicated for use in IAI as well as other types of infections. Although the Study for Monitoring Antimicrobial Resistance Trends (SMART) has documented the *in vitro* activity of ertapenem and several comparators against gram-negative pathogens of IAI (and, since late 2009, urinary tract infections), to-date SMART has not included anaerobic isolates. This study was undertaken to determine the *in vitro* activity of ertapenem and comparators commonly used to treat anaerobic infections against a large collection of anaerobes isolated relatively recently in Europe.

Materials & Methods

- 974 anaerobic isolates collected in 2010-2011 from a variety of specimen types (including, but not limited to, IAI) in the UK, Germany, France, Hungary, Czech Republic, and Belgium were tested at the IHMA central laboratory in Schaumburg, IL, USA using CLSI agar dilution methodology. [1]
- Quality controls (QC) were performed on each day of testing using appropriate ATCC control strains, following CLSI guidelines. Results were included in the analysis only when corresponding QC results were within the acceptable ranges [2].
- MICs for ertapenem, cefoxitin (gram-negatives only), clindamycin, meropenem, metronidazole, penicillin (gram-positives only), piperacillin-tazobactam, and tigecycline were interpreted using EUCAST and CLSI guidelines [2,3]; however, FDA breakpoints were used in the "CLSI" analysis for tigecycline because CLSI breakpoints do not exist. The following table summarizes the MIC breakpoints (mg/L) that were used for the susceptible category:

	EUCAST *C. difficile*	EUCAST All others	CLSI All	FDA All
Ertapenem	-	≤1	≤4	-
Cefoxitin	-	-	≤16	-
Clindamycin	-	≤4	≤2	-
Meropenem	-	≤2	≤4	-
Metronidazole	≤2*	≤4	≤8	-
Penicillin	-	≤0.25	≤0.5	-
Piperacillin-Tazobactam	-	≤8	≤32	-
Tigecycline	≤0.25*	-	-	≤4

* Epidemiologic cutoff; no clinical breakpoints

References

1. Clinical and Laboratory Standards Institute. 2012. Methods for Antimicrobial Susceptibility Tests of Anaerobic Bacteria; Approved Standard—Eighth Edition. CLSI Document M11-A8. Wayne, PA.
2. Clinical and Laboratory Standards Institute. 2013. Performance Standards for Antimicrobial Susceptibility Testing; Twenty-Third Informational Supplement. CLSI Document M100-S23. Wayne, PA.
3. European Committee on Antimicrobial Susceptibility Testing (EUCAST). 2013. Breakpoint tables for interpretation of MICs and zone diameters, version 3.1, http://www.eucast.org.

Acknowledgements

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Results

Table 1. MIC_{50} and MIC_{90} (mg/L) by species.

	n	Ertapenem MIC_{50}	Ertapenem MIC_{90}	Cefoxitin MIC_{50}	Cefoxitin MIC_{90}	Clindamycin MIC_{50}	Clindamycin MIC_{90}	Meropenem MIC_{50}	Meropenem MIC_{90}	Metronidazole MIC_{50}	Metronidazole MIC_{90}	Penicillin MIC_{50}	Penicillin MIC_{90}	Pip-Tazo MIC_{50}	Pip-Tazo MIC_{90}	Tigecycline MIC_{50}	Tigecycline MIC_{90}
B. fragilis	265	0.12	0.5	4	16	0.5	>8	≤0.06	0.25	1	4	NT	NT	0.25	1	0.25	1
Other *Bacteroides* spp.	135	0.25	1	8	32	1	>8	0.12	0.5	0.5	2	NT	NT	1	16	0.12	1
C. difficile	151	2	4	NT	NT	2	>8	1	2	0.5	2	1	4	4	8	≤0.06	≤0.06
Other *Clostridium* spp.	97	≤0.03	0.5	NT	NT	0.5	4	≤0.06	0.5	1	2	≤0.25	1	≤0.06	4	0.12	0.5
Prevotella spp.	169	0.12	0.25	≤2	8	≤0.25	>8	≤0.06	0.12	0.5	2	NT	NT	≤0.06	1	≤0.06	0.5
Peptostreptococcus spp.	72	≤0.03	0.25	NT	NT	≤0.25	≤0.25	≤0.06	0.25	≤0.125	0.5	≤0.25	≤0.25	≤0.06	0.12	≤0.06	≤0.06
Finegoldia magna	46	≤0.03	0.12	NT	NT	0.5	>8	≤0.002	0.004	0.25	1	≤0.25	≤0.25	≤0.06	0.12	≤0.06	≤0.06
Peptoniphilus asaccharolyticus	21	≤0.03	0.12	NT	NT	≤0.25	>8	≤0.06	≤0.06	0.25	0.5	≤0.25	≤0.25	≤0.06	≤0.06	≤0.06	≤0.06
Anaerococcus prevotii	18	≤0.03	0.25	NT	NT	≤0.25	>256	≤0.06	0.12	0.25	1	≤0.25	1	≤0.06	0.25	≤0.06	≤0.06

NT= Not tested

Table 2. Susceptibility and MIC_{50} and MIC_{90} (mg/L) for all species combined.

Drug	EUCAST *C. difficile*	EUCAST Others	CLSI All	MIC_{50}	MIC_{90}
Ertapenem	-	96.0%	97.9%	0.12 mg/L	2 mg/L
Cefoxitin	-	-	94.2%[1]	4 mg/L	16 mg/L
Clindamycin	-	77.1%	75.3%	0.5 mg/L	>8 mg/L
Meropenem	-	97.2%	98.7%	≤0.06 mg/L	1 mg/L
Metronidazole	98.7%[2]	100%	100%	0.5 mg/L	2 mg/L
Penicillin	-	65.2%[3]	71.7%[3]	≤0.25 mg/L	2 mg/L
Piperacillin/Tazobactam	-	97.0%	99.7%	0.12 mg/L	8 mg/L
Tigecycline	98.0%[2]	-	99.5%[4]	≤0.06 mg/L	0.5 mg/L

[1]Gram-neg only
[2]Epidemiologic cutoff; no clinical breakpoints
[3]Gram-pos only
[4]FDA breakpoint; no CLSI breakpoint exists

Figure 1. Ertapenem percent susceptible, comparing EUCAST and CLSI breakpoints (a EUCAST breakpoint does not exist for *C. difficile*).

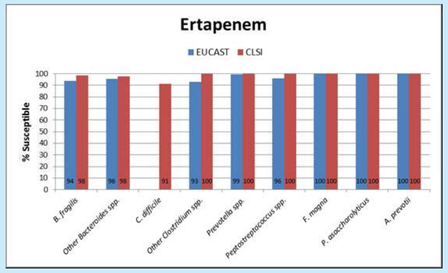


Figure 2. Cefoxitin percent susceptible (only gram-negative organisms were tested, and only CLSI breakpoints exist).

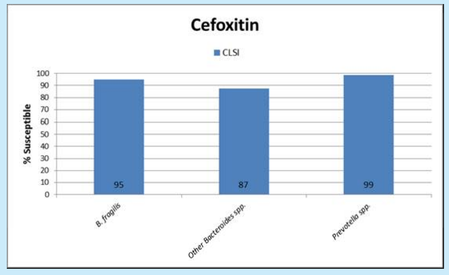


Figure 3. Clindamycin percent susceptible, comparing EUCAST and CLSI breakpoints (a EUCAST breakpoint does not exist for *C. difficile*).

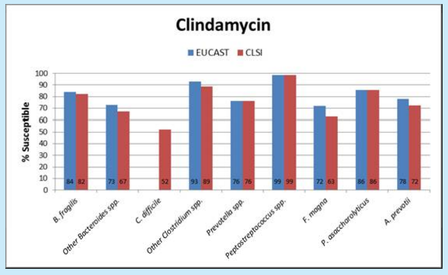


Figure 4. Meropenem percent susceptible, comparing EUCAST and CLSI breakpoints (a EUCAST breakpoint does not exist for *C. difficile*).

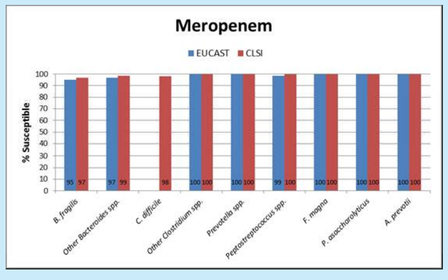


Figure 5. Metronidazole percent susceptible, comparing EUCAST and CLSI breakpoints (the EUCAST breakpoint for *C. difficile* is an epidemiologic cutoff; no clinical breakpoint exists).

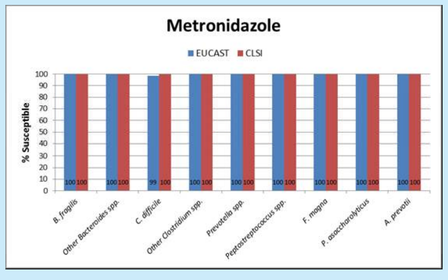


Figure 6. Penicillin percent susceptible, comparing EUCAST and CLSI breakpoints (only gram-positive organisms were tested; a EUCAST breakpoint does not exist for *C. difficile*).

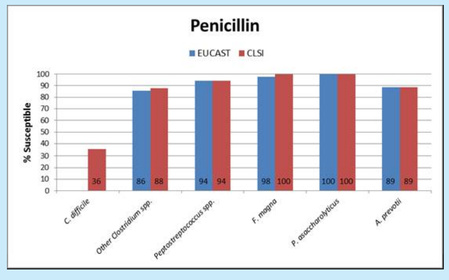


Figure 7. Piperacillin-tazobactam percent susceptible, comparing EUCAST and CLSI breakpoints (a EUCAST breakpoint does not exist for *C. difficile*).

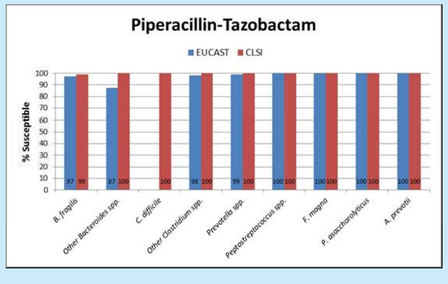
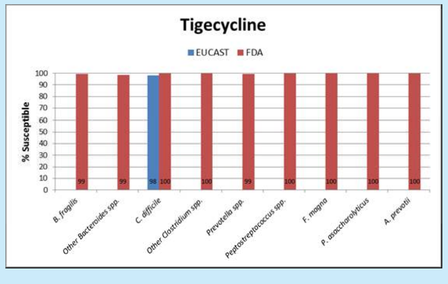


Figure 8. Tigecycline percent susceptible, comparing EUCAST and FDA breakpoints (the EUCAST breakpoint for *C. difficile* is an epidemiologic cutoff; no clinical breakpoint exists).



Conclusions

- All drugs tested other than clindamycin and penicillin inhibited ≥96% of the combined isolates. Even when looking at species and species groups separately vs. all agents except clindamycin and penicillin, only "other *Bacteroides* spp." showed susceptibility <90% (for cefoxitin and piperacillin-tazobactam).
- Although EUCAST breakpoints were lower than CLSI's for all drugs except clindamycin, % susceptible values for all tested species combined were within 0-7 percentage points of each other. When looking at species separately, the biggest differences between EUCAST and CLSI % susceptible values were found for *F. magna* vs. clindamycin (9 percentage points) and for "other *Bacteroides* spp." vs. tigecycline (13 percentage points).
- Ertapenem's *in vitro* activity against this collection of anaerobes was essentially equivalent to that of meropenem, metronidazole, piperacillin-tazobactam, and tigecycline.